

# Partial Disruption of Fear Conditioning in Rats With Unilateral Amygdala Damage: Correspondence With Unilateral Temporal Lobectomy in Humans

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Conditioned fear in rats was assessed for the effects of pretraining amygdala lesions (unilateral vs. bilateral) across unconditioned stimulus (US) modalities (white noise vs. shock). In contrast to sham controls, unilateral amygdala lesions significantly reduced conditioned freezing responses, whereas bilateral amygdala lesions resulted in a nearly complete lack of freezing to both the conditioned stimulus (CS) and the context. The lesion effects were more pronounced for CS conditioning but were consistent across US modalities. It was concluded that white noise can serve as an effective US and that unilateral amygdala lesions attenuate but do not eliminate conditioned fear in rats. The results support our interpretation of a recent fear conditioning study in humans (K. S. LaBar, J. E. LeDoux, D. D. Spencer, & E. A. Phelps, 1995).

In a recent study, we demonstrated impaired fear conditioning in human patients with unilateral temporal lobe resection to control medically refractory epilepsy (LaBar, LeDoux, Spencer, & Phelps, 1995). These patients were deficient in producing conditioned responses (CRs) on paired conditioned stimulus (CS)–unconditioned stimulus (US) acquisition trials. This result was consistent across both simple and conditional discrimination tasks and could not be attributed to deficits in declarative memory or sensorimotor function. On the basis of animal models of conditioned fear (for reviews, see Davis, 1992, 1994; Fanselow, 1994; Kapp, Wilson, Pascoe, Supple, & Whalen, 1990; LeDoux, 1990, 1995a, 1995b), we suggested that the impairment may be related to the patients' sustained damage to the amygdala, although the epileptiform activity and subsequent surgical excision encompassed other structures in the medial temporal lobe.

In contrast to typical animal models, however, the LaBar et al. (1995) study differed in several ways, including that (a) a loud white noise burst was used as the US, and (b) the extent of amygdala damage was predominantly unilateral. As a consequence, we did not have direct support for our interpretation of the human study when extrapolating from the existing animal literature. Most neurobiological work in this area has relied on the use of footshock as a US, despite the fact that the afferent neural pathways signaling footshock elicitation are not well-understood (Davis, 1992). An early study by Lyon (1964) used a loud noise US to examine the role of midbrain structures in avoidance conditioning, and more recently, white noise has been shown to serve as an effective unconditioned

fear stimulus in hypoalgesia and startle experiments (e.g., Leaton & Cranney, 1990; Helmstetter & Bellgowan, 1994). Few studies have systematically examined the effects of unilateral lesions. In a preliminary report, McLaughlin, Murphy, Penney, Chachich, and Powell (1994) did not find an effect of unilateral amygdala lesions on conditioned bradycardia in rabbits. However, Coleman-Meschke and McGaugh (1995a, 1995b, 1995c) have found robust effects of unilateral right amygdala inactivation on retention of passive avoidance in rats.

In the present experiment, we examined the effects of US modality (white noise vs. footshock) and pretraining amygdala lesions (unilateral vs. bilateral) on conditioned fear in the rat. Conditioning to both an explicit CS and context were examined with freezing as a dependent measure. This study will directly compare the effects of amygdala lesions across US modalities and will assess whether unilateral amygdala lesions impair conditioned fear responding in a manner equivalent to that seen in the human study (LaBar et al., 1995).

## Method

### *Animals and Surgical Procedure*

Male Sprague-Dawley rats (Hilltop Labs, Scottsdale, PA), weighing 300–325 g on arrival, were housed in pairs in a colony room. They were maintained on a 12-hr light–dark cycle and were given free access to lab chow and water. Approximately 1 week after arrival, the rats were assigned to one of two conditioning procedures (white noise US or footshock US) and one of four surgical groups (unilateral amygdala lesion, bilateral amygdala lesion, unilateral sham lesion, bilateral sham lesion). Thirty-eight rats were trained on the noise paradigm (14 unilateral amygdala lesions: 7 left hemisphere, 7 right hemisphere; 6 bilateral amygdala lesions; 18 sham lesions), and 37 rats were trained on the shock paradigm (16 unilateral amygdala lesions: 8 left hemisphere, 8 right hemisphere; 9 bilateral amygdala lesions; 10 sham lesions). The animals were anesthetized with ketamine (100 mg/kg ip) and Rompun (5 mg/kg ip) and placed in a stereotaxic frame. The skull was exposed and a hole was made over the amygdala(e) with a dental drill. Two electrode drops were used for each amygdala lesion with the

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following coordinates (in mm) relative to bregma: (1) AP = -2.3, ML =  $\pm$ 4.8, DV = -8.4; (2) AP = -2.8, ML =  $\pm$ 5.2, DV = -8.5. Lesion coordinates were provided by Kathleen R. Melia. Electrolytic amygdala lesions were made by passing 1 mA direct (anodal) current for 15 s through a 0.25-mm diameter electrode (Kopf NE-300) insulated to within 0.50–0.75 mm of its tip. Sham lesions were produced in an identical manner, except that the electrode was placed 1 mm ventral to the above coordinates and no current was passed through the electrode. The wound was sutured, and animals recovered under a heat lamp before returning to the colony room. A few pseudoconditioned nonlesion controls were also run, but their data will not be reported here (see Phillips & LeDoux, 1994, for pseudoconditioned control group data). For purposes of analysis, bilateral and unilateral sham-operated animals were combined to form one control group.

### Apparatus and Training Procedure

Behavioral testing began approximately 1 week following surgery. The conditioning procedures have been previously described (Phillips & LeDoux, 1992, 1994, 1995) and will only be summarized here. Animals run on the noise and shock paradigms were tested separately in individual conditioning chambers located in neighboring sound-insulated rooms. Conditioning took place in a rodent chamber (Coulbourn Instruments, Lehigh Valley, PA, Model E10-10) housed within a sound-attenuating cubicle. The chamber contained a wall-mounted speaker through which the tone CS (signal generator Model S81-06) and noise US (white noise generator Model S81-02) were delivered, and a grid floor (Model E10-10SF) through which the shock US was delivered (shocker Model E13-08). Delivery of all stimuli was controlled by a data acquisition board attached to an IBM-compatible personal computer. For all experimental groups, the CS was a 10-kHz, 75-dB tone (20-s duration). For rats in the noise paradigm, the US was a white noise burst (1-s duration) amplified to 110 dB by audio amplifiers (Model S82-24 and Radio Shack Model MPA-30). For rats in the shock paradigm, the US was a 0.5-mA footshock (0.5-s duration). These parameters have been shown to provide reliable conditioning in previous studies (LaBar & LeDoux, 1994; Phillips & LeDoux, 1992). The intertrial interval varied from 60 s to 120 s for all animals.

On Day 0, the animals were adapted to the conditioning chamber for 20 min with no stimuli being presented, and their general activity levels were observed on this day. On Days 1 and 2 (acquisition), they received two conditioning trials per day consisting of CS-US presentations in which the US coterminated with the CS. On Days 3–7 (extinction), the rats were given two conditioning trials per day in which the CS was presented by itself.

Freezing behavior (Blanchard & Blanchard, 1972; Bouton & Bolles, 1980; Fanselow, 1980; McAllister & McAllister, 1971) was used as the dependent measure of conditioning. Stopwatches were used to record the amount of freezing during the 20-s CS presentation. Additionally, the amount of freezing during the 20-s interval immediately preceding CS onset was recorded as a measure of contextual conditioning (Phillips & LeDoux, 1992, 1994, 1995). Only data from the first trial of each day was analyzed to avoid possible confounding effects of the CS and US presentation on responses measured during the second trial of each day.

### Histology

After completing the behavioral testing, lesioned animals were given an overdose of sodium pentobarbital (120 mg/kg ip) and were transcardially perfused with 200 ml of physiological saline followed by 200–300 ml of 10% buffered formalin. The brains were extracted from the skulls, postfixed for 24 hr in buffered formalin, and stored in a 15%

(wt/vol) sucrose-saline solution. The brains were frozen and cut into 40- $\mu$ m coronal sections on a microtome. Every third section in the vicinity of the amygdala was mounted on a gelatin-coated slide, dried, and stained with 5% cresyl violet. Lesion reconstruction was performed by tracing lesion boundaries under a light microscope onto serial atlas sections (Paxinos & Watson, 1986).

## Results

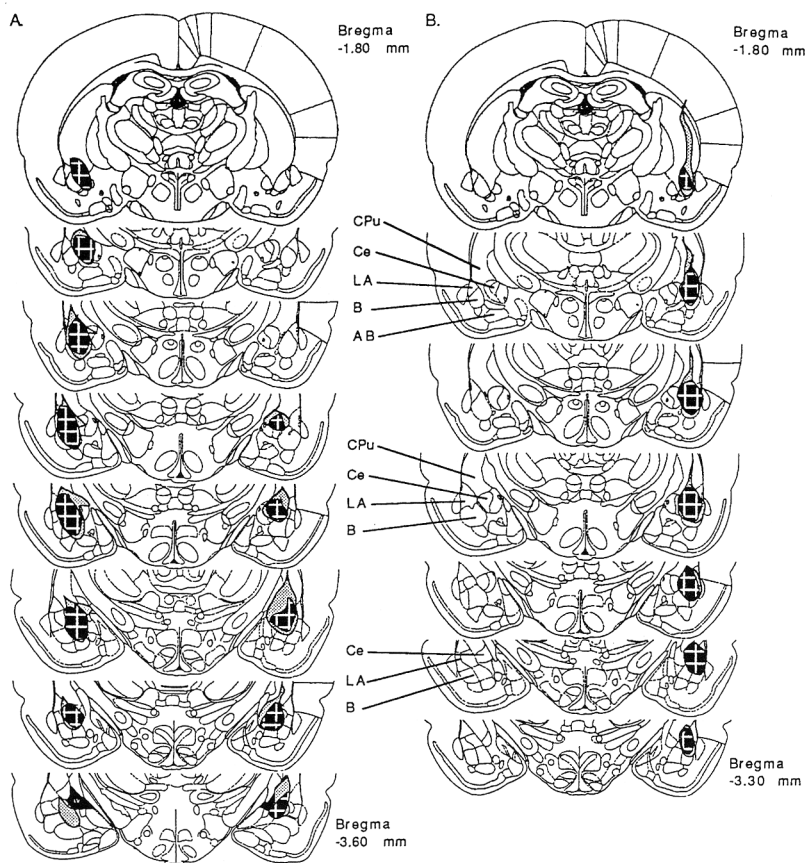
### Histological Results

Figure 1 illustrates typical unilateral and bilateral amygdala lesions. Lesions were centered primarily on the lateral nucleus and extended ventrally into the basolateral nucleus and medially into the central nucleus. Most animals also had some damage to the amygdalostratial zone and ventral portions of the caudate in the vicinity of the electrode track. Animals in which the lesion extended laterally into the perirhinal cortex were excluded from the study. Fifteen rats (6 bilateral, 5 left unilateral, 4 right unilateral) in the noise paradigm and 13 rats (6 bilateral, 4 left unilateral, 3 right unilateral) in the shock paradigm had accurately-placed lesions and were used in the statistical analysis.

### Behavioral Results

An alpha level of .05 was used for all statistical analyses. Two-way (Hemisphere  $\times$  Day) analyses of variance (ANOVAs) computed for the unilateral lesion group did not reveal any significant differences between left- and right-hemisphere amygdala-lesioned rats in CS or contextual conditioning, so these animals were combined to form one unilateral lesion group. This result held for rats run on both the noise and shock US paradigms. Three-way ANOVAs, with testing day (Day 1–7) as a within-subjects variable, and group (bilateral amygdala lesion, unilateral amygdala lesion, sham lesion) and US modality (noise, shock) as between-subjects variables, were computed for CS and contextual conditioning measures separately and are reported below.

**CS Conditioning.** Conditioned freezing to the CS is illustrated by group in Figure 2. A three-way ANOVA revealed a significant Group  $\times$  Day interaction,  $F(12, 300) = 9.52, p < .0005$ . In addition, the main effect of US,  $F(1, 50) = 4.88, p = .032$ ; group,  $F(2, 50) = 29.72, p < .0005$ ; and day,  $F(6, 300) = 28.40, p < .0005$ , were all significant. The main effect of US indicates that, overall, rats run with a shock US froze more to the CS than rats run with a loud noise US. Follow-up post hoc Tukey-Kramer honestly significant difference (HSD) tests on the Group  $\times$  Day interaction are summarized in Table 1. In general, for rats run on both the noise and shock paradigms, CS conditioning was greatest in the sham-operated control group, intermediate in the unilateral amygdala-lesioned group, and minimal in the bilateral amygdala-lesioned group. These differences in levels of conditioning were most consistently evident on Day 3, but began to develop on Day 2 and in some cases extended throughout extinction (see Table 1). Post hoc planned-comparison *t* tests comparing conditioning on Day 3 versus Day 1 revealed significant acquisition effects in all groups (all *ps* < .05) except the bilateral amygdala-lesioned group. This result was corroborated by post hoc one-way



**Figure 1.** Representative anatomical reconstruction of (A) bilateral and (B) unilateral amygdala lesions. Areas with crosshatching indicate tissue loss. Areas with stippling indicate surrounding gliosis. Reconstructions are presented on serial atlas sections derived from Paxinos and Watson (1986). AB = accessory basal nucleus of the amygdala; B = basal nucleus of the amygdala; Ce = central nucleus of the amygdala; CPu = caudate putamen; LA = lateral nucleus of the amygdala.

ANOVAs computed for each group separately, which showed that the bilateral amygdala-lesioned group was the only one without a significant polynomial trend in the data over time.

**Contextual conditioning.** Conditioned freezing responses to the context are depicted by group in Figure 3. A three-way ANOVA showed a significant Group  $\times$  Day interaction,  $F(12, 300) = 3.31, p < .0005$ , and significant main effects of group,  $F(2, 50) = 10.73, p < .0005$ , and day,  $F(6, 300) = 5.90, p < .0005$ . The main effect of US was not significant. In contrast to the CS conditioning results presented above, US modality did not have a significant effect on contextual conditioning.

Follow-up post hoc Tukey-Kramer HSD tests were computed to examine the Group  $\times$  Day interaction (see Table 2). Contextual conditioning was greatest in the sham-operated control group, intermediate in the unilateral amygdala-lesioned group, and lowest in the bilateral amygdala-lesioned group. The group differences were most prominent on Days 3 and 4, although there were some marginal differences on other days. These effects are not as robust as those observed for CS conditioning, presumably because of the comparatively reduced amount of freezing supported by contextual cues. Post hoc planned-comparison *t* tests computed for conditioning on

Day 3 versus Day 1 revealed significant acquisition effects in all groups (all  $ps < .05$ ) except the unilateral lesioned group in the noise paradigm and the bilateral lesioned group in both paradigms. Follow-up one-way ANOVAs by group revealed significant polynomial trends in the data over time for all groups except the bilateral amygdala-lesioned rats, demonstrating that these animals did not acquire conditioned responses to the context during the experiment.

## Discussion

In the present experiment, we examined the effects of US modality and compared the consequences of unilateral and bilateral amygdala lesions on conditioned fear in rats. Rats run with a shock US froze more to the CS than rats run with a loud noise US, but both groups demonstrated significant conditioned fear acquisition, and US modality had no effect on contextual conditioning. Thus, it appears that both a loud white noise and a footshock can serve as effective USs for conditioned freezing behavior, and, given that there were no Group  $\times$  US interactions, amygdala lesions affected performance similarly irrespective of US modality.

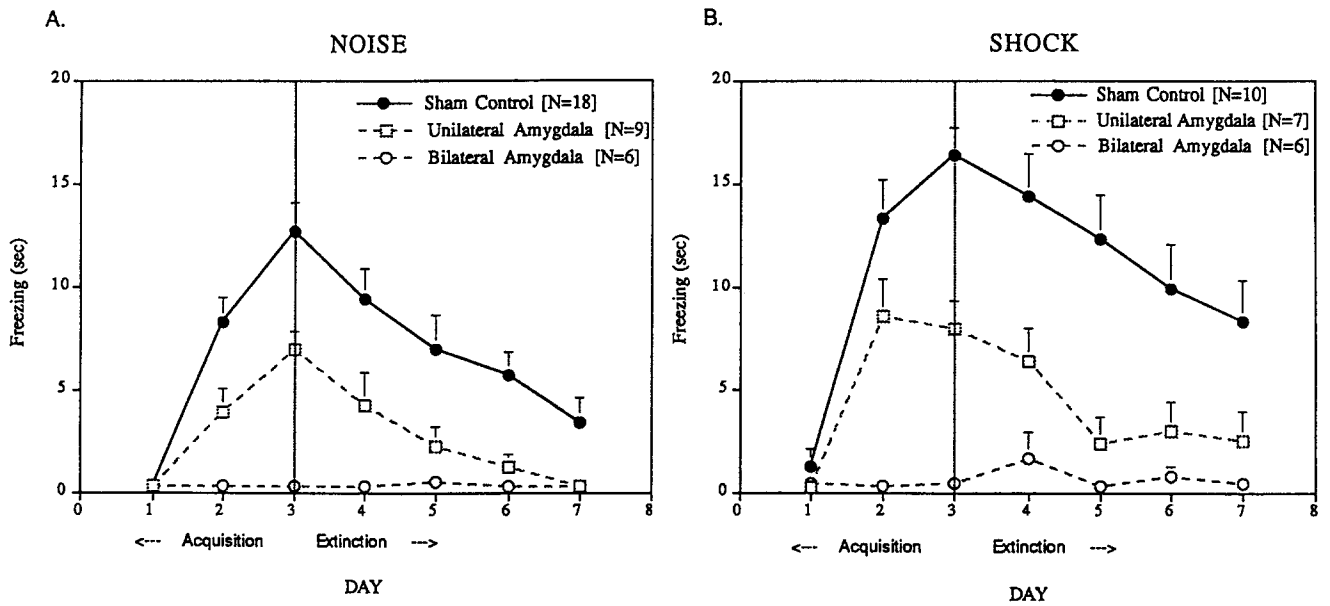


Figure 2. Effects of unilateral and bilateral amygdala lesions on conditioned freezing to the conditioned stimulus. Values represent group means (+ SEM). A: Acquisition and extinction for rats conditioned with a white noise unconditioned stimulus (US). B: Acquisition and extinction for rats conditioned with a footshock US.

In general, rats with unilateral amygdala lesions displayed attenuated conditioned responses in comparison to sham-operated controls, whereas rats with bilateral amygdala lesions showed no evidence of conditioning to either the CS or the context. The group differences were more pronounced for CS conditioning than for contextual conditioning, presumably because of the greater overall amount of conditioning supported by the CS. We propose two hypotheses regarding the response decrement observed in the unilateral lesioned group. First, it is possible that a learning mechanism was impaired in these rats, such that less associative strength accrued to the CS

and contextual cues, although not to the extent as that observed in the bilateral lesioned group. Second, it is possible that in the unilateral lesioned animals the machinery for making CS-US associations was still functional but that the expression of the learned associations was attenuated. One way to test these alternatives is to examine the effects of posttraining unilateral lesions on the expression of an already-learned CS-US association. Posttraining bilateral lesions of the amygdala do impair the expression of acquired CRs (Campeau & Davis, 1995; Kim & Davis, 1993; but for constraints on this effect in avoidance conditioning, see Liang, 1991; Liang et al., 1982; Parent, Avila, & McGaugh, 1995; Parent, Quirarte, Cahill, & McGaugh, 1995; Parent, Tomaz, & McGaugh, 1992; Parent, West, & McGaugh, 1994). Thus, bilateral amygdala lesions can impair both the acquisition and expression of conditioned responding (cf. Helmstetter, 1992); whether this result holds for unilateral amygdala lesions remains to be tested. In addition, it would be valuable to look at the unconditioned responses to the US for the unilateral group. Because we used freezing as a dependent measure, we could not obtain an independent assessment of freezing to the US during the experiment without contamination by contextual or CS freezing. Future experiments utilizing another dependent measure with a shorter refractory time course or freezing studies examining US sensitivity in a different context after extinction would assess whether the expression of unconditioned responding is also attenuated following unilateral ablation.

Coleman-Mesches and McGaugh (1995a, 1995b, 1995c) found that temporary unilateral amygdala inactivation disrupts retention of passive avoidance in rats. In this line of research, pretraining microinjection of lidocaine as well as posttraining

Table 1  
Post Hoc Tukey-Kramer HSD Results for CS Conditioning

Group comparison	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Bilateral amygdala vs. sham control						
Noise	**	**	**	*	*	
Shock	**	**	**	**	**	*
Bilateral amygdala vs. unilateral amygdala						
Noise		*				
Shock	*	**				
Sham control vs. unilateral amygdala						
Noise	*	*	*		*	
Shock		**	*	**	*	<i>ms</i>

Note. There were no significant differences on Day 1. HSD = honestly significant difference; CS = conditioned stimulus; *ms* = marginally significant: .05 < *p* < .10. \**p* < .05. \*\**p* < .01.

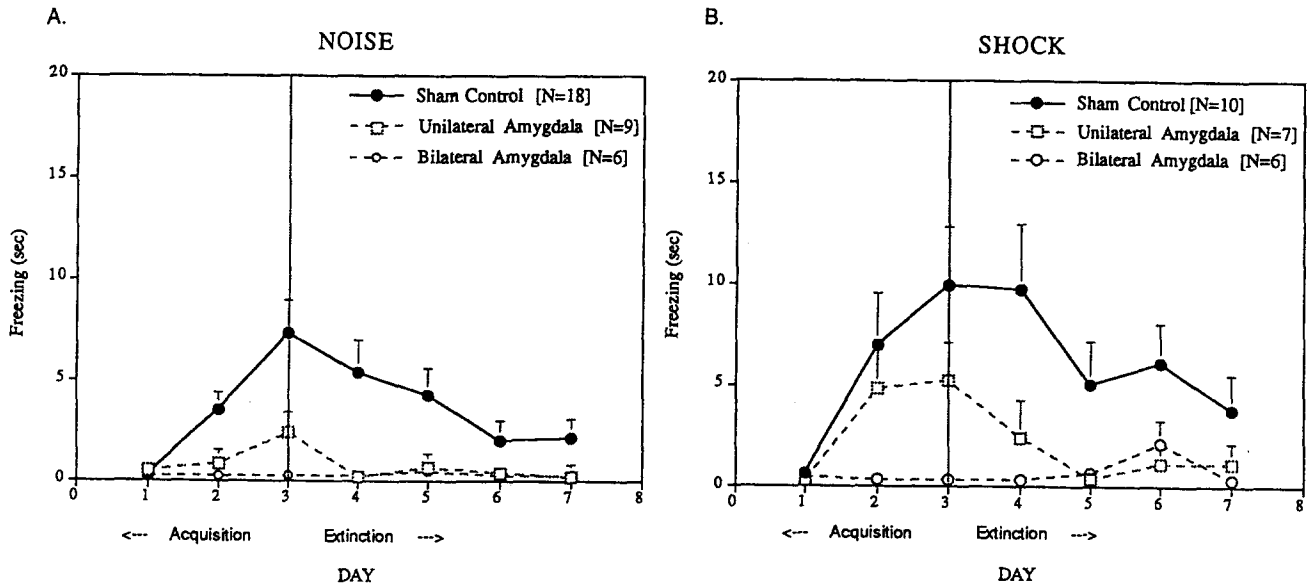


Figure 3. Effects of unilateral and bilateral amygdala lesions on conditioned freezing to the context. Values represent group means (+ SEM). A: Acquisition and extinction for rats conditioned with a white noise unconditioned stimulus (US). B: Acquisition and extinction for rats conditioned with a foot-shock US.

microinjection of either lidocaine or muscimol impaired retention latencies if administered bilaterally or unilaterally to the right hemisphere. Pretraining unilateral manipulations, however, did not significantly affect acquisition. In contrast to these findings, in the present study we found impairments in the unilateral group in acquisition as well as extinction, and we did not find a hemispheric specialization effect of unilateral ablation. The lack of hemispheric asymmetry may be due to the small sample size in the current study. However, in the LaBar et al. (1995) human study with a larger population sample, we

also did not report hemispheric effects on conditioning. These contrasting results may be related to differences in asymmetries between avoidance and fear conditioning or to differences in the permanence of the lesion, as hemispheric effects may be more subtle and more readily probed with reversible lesions. Some hemispheric specialization in conditioning has been reported in normal human subjects, as reviewed by Hugdahl (1984, 1995).

In other experiments on fear conditioning and emotional behavior, unilateral amygdala manipulations have yielded mixed results. Good and Westbrook (1995) reported significant impairment of conditioned fear and hypoalgesia by unilateral right amygdala injections of morphine. In unpublished data, Campeau, Miserendino, and Davis have found significant decrements in fear-potentiated startle in rats with either pre- or posttraining unilateral amygdala lesions (M. Davis, personal communication, April 12, 1995). McLaughlin et al. (1994), however, showed no consistent effects of unilateral amygdala lesions on conditioned bradycardia. In an early study, Downer (1961) demonstrated that unilateral amygdala lesions in a split-brain monkey were capable of producing a Klüver-Bucy syndrome but only in reaction to visual stimuli when visual input was restricted to the hemisphere ipsilateral to the lesion. More recently, rare cases of full (Ghika-Schmid, Assal, DeTribolet, & Regli, 1995) and partial (Bates & Sturman, 1995) Klüver-Bucy syndrome in humans with unilateral temporal lobe damage have been reported.

The unilateral amygdala lesion results in the present study support our interpretation of a set of conditioning experiments conducted on human temporal lobectomy patients (LaBar et al., 1995). In that study, unilateral temporal lobectomy subjects demonstrated impaired conditioned responses on paired

Table 2  
Post Hoc Tukey-Kramer HSD Results  
for Contextual Conditioning

Group comparison	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Bilateral amygdala vs. sham control						
Noise	<i>ms</i>	*				
Shock		*	*			
Bilateral amygdala vs. unilateral amygdala						
Noise						
Shock						
Sham control vs. unilateral amygdala						
Noise	<i>ms</i>	<i>ms</i>	*			
Shock					<i>ms</i>	

Note. There were no significant differences on Day 1. HSD = honestly significant difference; *ms* = marginally significant: .05 < *p* < .10.  
\**p* < .05.

CS-US acquisition trials, which we attributed to the amygdala damage sustained in these patients. There are several additional variables to consider, though, which may have contributed to the impairment in this population: (a) The history of epileptiform activity and subsequent surgical resection extended to adjacent structures in the medial temporal lobe; (b) the functional integrity of the contralateral hemisphere in this type of patient population has been questioned (Daum, Channon, & Gray, 1992; Incisa della Rocchetta et al. 1995); and (c) in general, humans with unilateral damage in this region tend to show greater deficits than that seen in other species (see Aggleton, 1992). Further support for our interpretation regarding a specific role of the amygdala comes from a conditioning experiment on a rare human patient (SM-046) with more restricted bilateral amygdala damage (Bechara et al., 1995). In contrast to a patient with bilateral hippocampal damage (sparing the amygdala) and normal controls, SM-046 showed almost no conditioned fear responses. Interestingly, this pattern of results is similar to that reported in the bilateral amygdala-lesioned rats in the present study and is more severe than the deficit observed in either rats or humans with unilateral amygdala damage (LaBar et al., 1995; Results, present study).

In both of the human fear conditioning experiments (Bechara et al., 1995; LaBar et al., 1995), a loud noise served as the US. Previous reports have suggested that white noise and mild electric shock support equivalent levels of conditioning in both humans and animals (e.g., Johnson & Helmstetter, 1994; Leaton & Cranney, 1990). We have reached similar conclusions in the present rat study using conditioned freezing as a dependent measure, except for some response enhancement to the CS for rats conditioned to a shock US. Most neurobiological animal studies have relied solely on the use of a footshock US, although a variety of CSs and dependent measures of conditioning have been explored. This can be viewed as limiting in several ways. First, because the afferent pathways mediating a footshock US remain elusive in the neural architecture of fear conditioning (Davis, 1992), it may be useful to consider other USs with shorter relays or whose stimulus properties are more well-defined. In this vein, Cahill and McGaugh (1990) have suggested that the amygdala's contribution to fear conditioning may be particularly sensitive to the arousing properties of the US. Second, conditioning experiments in which a visual or auditory CS is paired with a footshock US require that the animal perform a cross-modal association. Cross-modal associations outside of the conditioning domain have been shown to be impaired by amygdala lesions (Murray & Mishkin, 1985), although the specific contribution of the amygdala is now being reevaluated (Goulet & Murray, 1995; Lee, Reed, Meador, Smith, & Loring, 1995; Nahm, Tranel, Damasio, & Damasio, 1993; Murray & Gaffan, 1994). This raises the question as to what extent the cross-modal requirement of previous conditioning tasks impaired performance. The present study demonstrates that amygdala lesions compromise conditioning by intramodal (auditory-auditory) associations in a similar manner (see also Bechara et al., 1995). Therefore, it is not likely that in previous experiments, subjects with amygdala damage were impaired critically by the cross-modal nature of the task. Finally, any comprehen-

sive theory of fear conditioning needs to be able to account for the variety of motivational stimuli present in the environment. The current study extends what is known about the role of the amygdala in this regard and supports neurobehavioral theories postulating a fundamental position for the amygdala in the mediation of conditioned fear associations.

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